IMI2 777363 – DRIVE

Development of Robust and Innovative Vaccine Effectiveness

WP4 – Framework for

analysis and study reports

# D4.6.2 Points to consider document on the interpretation of VE results

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|---|---|
| **Lead contributors** | Topi Turunen (1 – FISABIO) – original D4.6 |
| | Antonio Carmona (1 – FISABIO) – updated D4.6.2 |
| | Cintia Muñoz-Quiles (1 – FISABIO) – updated D4.6.2 |
| | Anke Stuurman (3 – P95) original D4.6 and updated D4.6.2 |
| **Other contributors** | Jos Nauta (13 – ABBOTT) – original D4.6 |
| | Riia Järvenpää (6-THL) – original D4.6 |
| | Josephine van Boxmeer (14 – SEQIRUS) – original D4.6 |
| | Paolo Bonanni (4 - UNIFI) – original D4.6 |
| | Margarita Riera (3 – P95) – original D4.6 |
| | Helene Bricout (12 – Sanofi) – updated D4.6.2 |
| | Ulrike Baum (6 – THL) – updated D4.6.2 |
| | Roberto Bonaiuti (4 – UNIFI) – updated D4.6.2 |
| | Miriam Levi (4- UNIFI/Local Health Authority Tuscany Centre) – original D4.6 and updated D4.6.2 |

## Document History

| Version | Date | Description |
|---|---|---|
| V1.0 | 13 Apr 2022 | First Draft for WP4 and WP7 review |
| V2.0 | 11 May 2022 | Implementation of WP4 and WP7 comments. Final version. |

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## Abstract

One of the objectives of the DRIVE (Development of Robust and Innovative Vaccine Effectiveness) project is to interpret the results of influenza vaccine effectiveness (IVE) studies and communicate their significance to different stakeholder groups.

There are some unique challenges related to estimating, interpreting and communicating the effectiveness of influenza vaccines. Their effectiveness (unlike that of most other vaccines) varies from season to season due to changes in the circulating viruses and the corresponding reformulations of the vaccine; and the level of matching between the vaccine strains and the influenza circulating strains. Effectiveness also depends on other variables such as the target population groups being vaccinated, which are determined by the vaccination programmes implemented in each country or region. On the other hand, a variety of study designs and adjustment methods to account for potential confounders are used to estimate IVE, each with their own strengths, limitations and statistical considerations that may influence the observed vaccine effectiveness.

Both naturally occurring variation in vaccine effectiveness and questions related to study design and analytical methods must be considered when evaluating and communicating IVE. The initial version of this document provided guidelines for interpretation of vaccine effectiveness results, which have been updated and complemented in the present version (D4.6.2).


# 1. Interpreting VE Results

The factors to be considered when interpreting IVE estimates are divided here into **external** and **study-specific factors**. Among the former are the annual vaccine composition recommendations by the World Health Organization (WHO) and their eventual match to the circulating viruses. The latter comprise different factors that may influence the IVE estimate of a given study or meta-analysis.

## 1.1 External factors

**Pattern of virus circulation and vaccine match**

The pattern of circulation of influenza viruses is not uniform across Europe; it differs in time and place. The WHO attempts to capture this by defining global influenza transmission zones[1], and differences are observed even on regional level within countries. The fact that the vaccine viral strain composition for trivalent and quadrivalent vaccines is the same for all of the northern hemisphere for the entire season, yet different viral types and subtypes may circulate at different times in different places, needs to be taken into account when interpreting vaccine effectiveness results. How well the circulating strains match the vaccine strains will have an effect on the observed VE; additional determinants such as egg adaptation of the vaccine viruses for vaccines manufactured using this technology are under investigation.

There is a need to consider IVE figures in context with the available molecular epidemiology data. For this purpose, it is helpful to stratify IVE estimates by virus type and subtype/lineage, and possibly clade, whenever possible. This will allow the comparison of vaccine effectiveness against matching vs. unmatching strains of the virus.

**SARS-CoV-2 virus circulation**

The COVID-19 pandemic, starting in March 2020, and the subsequent lockdowns and implementation of non-pharmaceutical interventions, drastically reduced the influenza circulation in Europe during the 2020/21 and 2021/22 season. Few lab-confirmed influenza cases were identified in the 2020/21 and 2021/22 season,

preventing the estimation of meaningful and informative IVE in those seasons. DRIVE established sample size thresholds to activate the IVE calculations, which were not met for the 2020/21 at any of the study sites or pooled analysis, except the cohort study. For the 2021/22 season, although a greater sample was achieved, the analysis threshold was barely met for several study sites.

The emergence of SARS-CoV-2 and interference with flu circulation, uncertainty of circulating strains due to reduced transmission and thus low flu detection in Europe must be taken into account in the interpretation of IVE estimates as we enter this new paradigm of SARS-CoV-2 and flu co-circulation.

**Waning immunity within season**

Concerns have been raised about intraseasonal waning of the protection conferred by influenza vaccination[2]. Potential explanations underlying waning protection of influenza vaccination have been discussed in the literature. One explanation is an intraseasonal evolving mismatch among the circulating viruses, but also the timing of vaccination, persistence of host seroprotection in general as well as the effect of immunosenescence especially in the elderly are being studied[3]. Current knowledge is still too limited for thorough understanding of the mechanisms.

There have been several attempts to quantify the waning effect of influenza vaccination during a season. Two methods have been proposed; firstly, to look at time between vaccination and disease onset and secondly to look at the calendar period of vaccination. To understand the size of the intraseasonal waning effect, a stratified analysis is suggested. The challenge is choosing the number of strata and the cut-off point(s). Sullivan et al. (2014)[4] showed that a small shift of the cut-off point could already have a major effect on the early and late VE estimates.

Even though methods are proposed to quantify the effect of waning immunity, it is important to consider all possible explanations for this effect when interpreting the VE estimates from different strata. When the wild virus significantly drifts during the flu season, that should at least be considered as part of the explanation. The effect is then likely to be seen across all age groups. Immunosenescence is typically related to elderly people and might be a possible explanation if the waning effect is only seen in the older age group. Lastly, the type of influenza vaccine used could be an explanation of the size of the waning effect. High-dose and adjuvanted vaccines are believed to be more immunogenic than normal dose non-adjuvanted vaccines[5] and a difference in the waning effect might be seen between these types of vaccines.

Another point to consider is that also the unvaccinated may encounter circulating influenza viruses during the season (with or without symptoms) and thus gain protection, or boosting of pre-existing immunity, from these natural encounters. Cumulative natural encounters in the population increase towards the end of the season, and immunity from these may be cross-protective and long-lasting relative to vaccine-induced immunity. This can be of particular importance when the influenza epidemic peak occurs late in the season, such as what was observed in the 2021/22 season. On the other hand, the highly susceptible unvaccinated might die at the beginning of the season, while the highly susceptible vaccinated might survive and are then prone for a second infection towards the end of the season. Altogether, the difference in disease susceptibility between the vaccinated and unvaccinated decreases during the season, which might lead to a decrease in the VE estimate over time. This highlights the need to account for the time between vaccination and disease onset, or, at minimum, to provide an exhaustive description of the influenza season under study (timing and evolution, circulating subtypes and strains), in parallel to the IVE estimates communication.

**Repeated vaccinations**

With numbers of annual influenza vaccinations increasing, the effect of repeated vaccination has gained interest. It has been postulated that repeated vaccinations can cause positive or negative interference[6]. Some studies have found signals of negative interference[7], but a meta-analysis[8] found no overall evidence that prior season vaccination impacts current season VE negatively. Nevertheless, more research on the subject is needed, and many studies look at the effect of vaccination in one or more previous seasons.

**COVID-19 vaccination effect on IVE**

In the current context, in which COVID-19 and influenza vaccines have been administered simultaneously in Europe (starting in the 2021/22 season) and the circulation of SARS-CoV-2 is likely to overlap with the influenza circulation (e.g., January to April 2022) it is key to assess the impact of COVID-19 vaccination in IVE estimation. So far, there has been little co-circulation of SARS-CoV-2 and influenza and therefore further research is needed to understand the impact of SARS-CoV-2 infection and COVID-19 vaccination on IVE.

The effect of joint vaccination with COVID-19 and influenza on VE estimates in TND studies has been studied[9,10] and should be acknowledged when interpreting VE results and designing VE studies based on the TND. However, DRIVE WP7 and EFPIA partners concluded that in the current landscape, with very high COVID-19 vaccine coverage in Europe, these considerations are not as relevant as in settings where COVID-19 vaccine coverage is lower. Consequently, DRIVE did not apply them in their protocols or SAP, but this is to be reassessed with time, as COVID19 vaccination could become an annual vaccination similarly to influenza vaccination and both COVID19 and influenza viruses might co-circulate in the coming years.

## 1.2. Study-specific factor

**Study setting & population**

It is important to relate VE to the population that was studied. Many IVE studies take place in a healthcare setting (e.g. a GP practice, hospital or a long-term care facility); the age and comorbidities of study subjects vary accordingly. A hospital setting generally reflects more severe forms of influenza as a GP setting.

Other studies use population-based registries of influenza diagnoses and vaccination information; in these cases, the source population and the swabbing practice may be broader and less well defined. In many cases, population groups will be underrepresented or absent from the study, e.g. due to differences in health-seeking behaviour.

Most studies consider the age group of the included subjects, and may present the VE estimates stratified by age and comorbidities. Vaccine effectiveness is typically better with children and healthy adults than with the elderly. However, even lower VE may be meaningful in the latter group since the incidence of serious outcomes such as hospitalization and death is greater, and vaccination is presumed to lower the severity of influenza illness even when it does not prevent it.

**Study design**

*Cohort studies*

When analysing findings from cohort studies, particularly if data are drawn from administrative databases, it is important to assess to what extent the vaccination records are expected to be complete (e.g. general practice databases may not capture vaccinations administered at other settings such as vaccination clinics). Completeness of data on outcomes should also be evaluated; identifying the outcome of interest could be a challenge, e.g. if cohort members can have access to multiple different health care providers[11].

Attention should be paid to healthcare seeking bias, which happens in case of differences in healthcare seeking behaviour between vaccinated and unvaccinated subjects, which could overwhelm a true vaccine effect. Vaccinated individuals may be more likely to seek care when experiencing acute respiratory infection-related symptoms or the opposite situation may occur, i.e. vaccinated patients may have less severe disease and thus be less likely to seek medical care. The WHO recommends researchers to determine the care-seeking patterns of the proposed study cohort. Researchers should be able to evaluate the proportion of outcomes that may be

missed due to seeking care outside of study facilities or at home self-treatment.

*Case-control studies*

In case-control studies attention should be paid to possible misclassification of vaccination status, especially when data regarding influenza vaccination are not collected through electronic medical records/registries. Another potential source of bias is the selection of the controls. They should be selected in such a way that the vaccine distribution among them is the same as that in the population that gave rise to the cases. If, for example, hospital-based controls are selected among cases hospitalized for a vaccine-preventable infection, vaccine distribution may be different from that of cases.

*The test-negative design (TND)*

The TND design is widely used as a method that allows minimizing confounding due to differences in healthcare seeking behaviour between vaccinated and unvaccinated individuals. However, the design is susceptible to other forms of bias. A source of bias may be represented by misclassification of disease in case influenza tests with imperfect sensitivity and specificity are applied. Findings from a study by Jackson and Rothman showed that when disease misclassification occurs, IVE estimates from the TND method are more biased than those from cohort or case-control designs[12]. However, the relative increase in bias is small when using highly sensitive and specific tests such as RT-PCR for diagnosing influenza, and the advantages in control of confounding by means of the TND method are likely to outweigh the bias due to outcome misclassification.

**Outcomes of study**

Non-specific outcomes, such as ILI and all-cause mortality that lack laboratory-confirmation, are sometimes used in IVE studies. Only a fraction of these outcomes is likely to be attributable to influenza. Interpreting IVE against these outcomes as a proxy for IVE against influenza disease leads to an underestimation of IVE.

Influenza virus causes a wide range of clinical disease and sequelae, therefore patients fulfilling ILI and SARI definitions and patients routinely swabbed by clinicians because of suspicion of influenza do not represent all influenza patients, and the hidden disease burden remains large. It should be noted that even a low VE against non-specific outcomes may indicate much higher absolute reduction in the disease burden than a high VE against a specific outcome[13].

**Vaccine characteristics**

*Valency*

Two types of formulations are available. The conventional trivalent vaccine contains both circulating influenza A viruses (H1N1 and H3N2 subtypes) and one influenza B virus. However, since trivalent vaccines have been shown to be less effective in case mismatches between the influenza B vaccine component and the circulating B strain occur, quadrivalent vaccines have been made available to provide a broader protection against circulating influenza B viruses[14]. The quadrivalent vaccines contain both influenza B lineages.

During the progress of the DRIVE project (season 2017/18 to 2021/22) we have observed a clear shift from trivalent to quadrivalent influenza vaccines. For instance, in the 2021/22 season, 2 out of the 10 licensed influenza vaccines were trivalent.

*Dosing*

In unprimed populations, such as children younger than 9 years and never vaccinated against influenza in the past, **two doses of inactivated split-virus and subunit vaccines** are recommended to achieve adequate immunogenicity. On the contrary, only **1 dose per season is sufficient when administering intra-nasal live-attenuated influenza vaccines** (LAIV) administered to children, except if not been previously vaccinated against seasonal influenza (in that case, children should receive a second dose 4 weeks after the first). This example highlights the variability in the dosing of influenza vaccines, particularly in children, which has to be taken into account when analyzing and interpreting IVE estimates.

Moreover, in the past few seasons, **high dose (HD) vaccines** have been introduced in the influenza vaccination programmes. HD influenza vaccines contain a higher concentration of antigen than the standard-dose influenza vaccines and are designed to produce stronger immune responses against the selected influenza vaccine strain. High dose vaccines are recommended to provide improved protection among older age groups in whom immune responses with regular standard-dose vaccines can be suboptimal. The High-dose influenza vaccine was first introduced in the EU during the 2019/20 season.

*Type of culture*

Two main types of viral cultures for influenza vaccines are mainly in use:

**Egg-based influenza vaccines**: The most common way that flu vaccines are made is using an egg-based manufacturing process that has been used for more than 70 years. Egg-based vaccine manufacturing is used to make both inactivated and live attenuated vaccine. The egg-based production process begins with the WHO Global Influenza Surveillance and Response System providing private sector manufacturers with candidate vaccine viruses (CVVs) grown in eggs per current FDA regulatory requirements. These CVVs are then injected into fertilized hen's eggs and incubated for several days to allow the viruses to replicate. The fluid containing virus is harvested from the eggs.

This production method requires large numbers of chicken eggs to produce vaccine and may take longer than other production methods[15].

**Cell-based influenza vaccines:** their production does not use flu viruses grown in eggs and, therefore, is not dependent on the supply of hen eggs. In addition, cell-based flu vaccines that use cell-based candidate vaccine viruses (CVVs) have the potential to offer better protection than traditional, egg-based flu vaccines. The viruses used to make cell-based vaccines may be more similar to circulating wild-type viruses than the ones used to produce egg-based vaccines, therefore might exhibit a higher effectiveness against the wild-type circulating flu viruses. The cell-based vaccine manufacturing process uses animal cells (e.g Madin-Darby Canine Kidney, or MDCK cells) as a host for the growing flu viruses[16].

While viruses used in previous seasons' cell-based vaccine have been grown in cells, prior to the 2019-2020 season some of the viruses provided to the manufacturer had been originally derived in eggs. For the 2021-2022 influenza season, all four flu viruses used in the cell-based vaccine are cell-derived, making the vaccine completely egg-free[17].

*Vaccine type*

Influenza vaccines currently marketed in the EU (2021/22) are classified into the following categories:

- Egg-based trivalent inactivated vaccine (eTIV)
- Egg-based quadrivalent inactivated vaccine (eQIV)

- Cell-based quadrivalent inactivated vaccine (cQIV)
- Egg-based intranasal quadrivalent live attenuated vaccine (eQLAIV)
- Egg-based Adjuvanted trivalent inactivated vaccine (aTIV)
- Egg-based Adjuvanted quadrivalent inactivated vaccine (aQIV)
- Egg-based High Dose quadrivalent inactivated vaccine (HD eQIV)
- Cell-based recombinant quadrivalent vaccine (cRQV)

**Split and subunit vaccines:** split vaccines consist of disrupted virus particles whereas subunit vaccines contain the major influenza virus surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), while lacking inner antigens and lipopolysaccharides. They are commonly used in TIV formulations, although they are now available for QIV vaccines as well.

**Intradermal vaccines:** beyond the standard intramuscular split vaccines, an intradermal influenza split vaccine is being administered in some countries in adults (this vaccine is recommended from 18 years). The aim of the intradermal administration is to improve the immune response by activating other arms of the immune system. The high density of antigen presenting cells in the skin allows for antigen dose- sparing in adults (9 mg HA), whereas the elderly still need a normal dose of 15 mg HA.

**Adjuvanted vaccines:** Adjuvanted inactivated vaccines contain HA and NA purified antigens adjuvanted with MF59 (an oil- in-water emulsion which consists of biodegradable squalene oil droplets stabilized by non-ionic surfactants) or AS03 (squalene and α-tocopherol). Studies indicate a better protection conferred by adjuvanted vaccines in the elderly[18, 19]. Adjuvanted vaccines are generally recommended for the elderly and high-risk patients. Therefore, patients who receive adjuvanted vaccines are generally older, with comorbidities and with reduced functional status.

**Intranasal vaccine:** intranasal vaccines contain the live-attenuated influenza virus, they have been approved in the EU/EEA for children and adolescents (2-17 years of age). All live attenuated influenza vaccines currently available are quadrivalent combination vaccines containing two influenza A strains and two influenza B strains as per the WHO recommendations.

**High-dose vaccines:** as described in the previous section. The High-dose influenza vaccine was first introduced in the EU during the 2019/20 season and its composition and dosing hast to be taken into account when interpreting IVE estimates in the older population.

**Recombinant protein vaccines**: There is a third production technology for influenza vaccines based on the production of recombinant proteins that mimic the structure of key proteins of the influenza virus. Recombinant influenza vaccines do not require having a candidate vaccine virus (CVV) sample to produce. Instead, hemagglutinin (HA) protein is created synthetically and used as an antigen. The gene coding for HA is combined with a baculovirus, resulting in a “recombinant” baculovirus. The role of the baculovirus is to transport the genetic instructions for producing the viral HA antigen into a host cell. To that aim, the recombinant baculovirus infects a cell line, and instructs the cells to produce the HA antigen. This antigen is grown in bulk, collected, purified, and then packaged as recombinant flu vaccine.

This production method does not require an egg-grown vaccine virus and does not use chicken eggs at all in the production process. This production process is the fastest because it is not limited by the selection of vaccine viruses that are adapted for growth in eggs or the development of cell-based vaccine viruses. The first recombinant protein influenza vaccine was introduced in the EU during the 2021/22 season.

**Future influenza vaccines based on mRNA technology:** the COVID-19 pandemic and the success of the mRNA-based COVID-19 vaccines has stimulated the development of mRNA vaccines for other vaccine-

preventable diseases, such as influenza. Conventional flu vaccines are grown in either chicken eggs or mammalian cells and also takes about six months to produce the millions of doses needed. Conversely, mRNA-based influenza vaccine design will require only the genetic sequence of the dominant virus, which significantly accelerates production time. The flexibility of mRNA technology and its rapid manufacturing time could potentially allow better strain match, greater reliability of supply, and the potential opportunity to improve upon the efficacy of current flu vaccines. Several mRNA-based influenza vaccines are currently in the pipeline (Moderna, Pfizer, Sanofi…)[20].

**Specificity & granularity**

As vaccine effectiveness differs from population to population (e.g. across age groups and depending on the presence of chronic conditions), VE results that are stratified by some of these factors are generally more informative than a single VE figure for the whole population. However, the granularity of the possible estimates is subject to the available sample size which in turn depends on both the severity of the season and the capacity of study sites to enrol patients in the study. Brand-specificity is a special case of granularity (please see Sample size and confidence intervals below and the sample size calculations in the DRIVE core protocols).

When a single VE percentage is used to describe the effectiveness of a vaccine in a large and varied population, the information should be considered in relation to the characteristics of that population, e.g. age distribution. Many surveillance systems capture predominantly older influenza patients which may drive the collective VE estimate towards lower values.

**Sample size and confidence intervals**

*Sample size*

Optimal sample size for single sites in a brand-specific vaccine effectiveness study depends on the study design (cohort design requires a larger sample size than case-control), influenza attack rate among unvaccinated persons (lower sample size with higher attack rate in cohort studies), the influenza vaccine coverage (overall, type-specific and brand-specific) and the vaccine effectiveness itself (if VE is low, sample size will need to be larger to detect the effect).

DRIVE has developed a sample size tool for free open use by scientific community. This web application allows to perform sample size calculations for cohort and test negative design studies on brand-specific and overall vaccine efficacy (accessible upon request through: https://shinyproxy.p-95.com/app/drivesamplesize).

For further discussion of sample size in the DRIVE perspective, please see the sample size calculations included in the DRIVE core protocols (D7.1.3 DRIVE Core TND protocol – D7.2.3 Core Register-Based Cohort protocol).

*Confidence intervals*

The uncertainty surrounding VE estimate is determined both by the variability of the data and the sample size. The less variation in the data and the larger the sample size, the lower the uncertainty around the VE estimate. Uncertainty is expressed using confidence intervals (CI). A 95%CI means there is 95% confidence that the interval will cover the true population VE.

VE estimates that are based on studies with low sample size and estimates with wide confidence intervals (low precision) should be interpreted with caution.

**Statistical analysis**

The statistical analysis of VE data must be consistent with the design of the study and should adjust for confounding (see below). The analysis of the data of a nested case-control design, for example, depends on the how the controls were sampled (by cumulative sampling or by density sampling). Another example is that in the analysis of the data of a case-cohort design the possible overlap between cases and controls (i.e. cases that were also sample as controls) must be allowed for. Confounding can be adjusted for either by multiple regression or by propensity scoring. In the first approach confounding is eliminated by including confounders as covariates in the regression model. Propensity scoring is an alternative to multiple regression to estimate the effect of treatments in observational studies. The goal is to balance observed covariates between treatment groups in order to mimic what happens in a randomized study. The two analysis methods yield similar results.

For the DRIVE approach to statistical analysis, please see the DRIVE Statistical Analysis Plan:

D4.4 Generic Statistical Analysis Plan: combining information on Influenza Vaccine Effectiveness across study sites
DRIVE SAP 2019/20
DRIVE SAP 2021/22

**Bias and confounding**

Bias occurs if the estimated VE differs systematically from the true VE. In VE studies there are many potential sources of bias. Examples are, amongst others, measurement error, selection bias and confounding. If the specificity of the diagnostic test for influenza infection is imperfect, the VE will be underestimated. Selection bias occurs when the subjects selected in the study are not representative for those eligible for the study. Confounding is a special type of bias, a mixing-up of effects, which distorts the relationship between vaccination and the risk of infection, and which therefore must be eliminated. A factor is a confounder if it is a cause of both vaccination and infection. 'A is a cause of B' should be interpreted in the non-strict sense that there is a statistical relationship directed from A to B. Thus, if the likelihood of being vaccinated increases with age, then age is said to be a cause of infection. Confounding can be reduced either in the design phase of the study, by matching or by making the source population more homogenous, or during the statistical analysis phase, by means of regression or propensity scoring. Not all types of bias can be eliminated in the statistical analysis. Measurement bias and selection bias, for example, cannot be eliminated statistically. These biases are best avoided during the design phase of the study.

Throughout the 5 years of the DRIVE project, we have discussed which confounders should be integrated into the generic protocol and collected by sites to ensure robust IVE estimates. EMA scientific advice was also sought by DRIVE partners on the required number of confounders and the relevance of a parsimonious analysis. For IVE analyses in the 2017/18 influenza season, DRIVE took advantage of data collected through existing infrastructures and selected confounders through model-building. In 2018/19, the first season for which a common protocol was developed and used, IVE estimates were adjusted for a fixed, elaborate set of confounders, namely age, sex, calendar time, presence of at least one chronic condition, pregnancy, number of hospitalizations or GP visits in the previous year and vaccination status in previous season. However, some sites were not able to collect all variables, either not at all or not for all subjects. This led to inconsistent confounder adjustment across sites and exclusion of subjects with missing values. To harmonize confounder adjustment and minimize data loss, the number of covariates adjusted for was decreased as of the 2019/20 season, retaining only age, sex and calendar time. Parsimonious confounder adjustment was supported by a post hoc analysis of DRIVE's 2018/19 data and was previously proposed by Lane et al. according to an analysis of data from the Victorian Influenza Sentinel Practice Network in Australia[21] and is in line with findings from the Canadian Sentinel Practitioner Surveillance Network (CSPSN)[22]. As a result, all sites were able to collect data on the confounders used in the main analysis 2019/20 and consequently data loss was reduced.

During the 2019/20 season, with the aim of gaining insight in potential unmeasured confounding of the IVE estimates for any vaccine against any influenza by age and setting, DRIVE calculated in a post-hoc analysis the E-values for the IVE estimates and for the limit of the CI closest to 0.

Next, DRIVE aimed to further explore the impact of potential confounders on IVE in the context of its multi-country TND network and to check through an in-depth multi-season secondary analysis if our previously chosen parsimonious confounder adjustment strategy could be justified. DRIVE colleagues constructed a directed acyclic graph (DAG) to map the relationship between influenza vaccination, medically attended influenza infection and confounders. We used DRIVE data from the 2018/19 and 2019/20 seasons to understand the role of covariates as predictors of vaccination status and case status, and to explore the effect of covariate adjustment on IVE point estimates. The results supported our previous decision on adopting parsimonious approach to confounder adjustment in TND studies, limited to adjusting for age, sex and calendar time[23]. This represents a useful lesson learnt for future IVE studies and IVE estimates interpretation.

For more information on bias and confounders, please also see Chapter 5 of the DRIVE D4.1: *"Framework for analysis of influenza vaccine effectiveness studies – last updated in March 2022"*.

**Crude VE estimates**

A crude vaccine effectiveness estimate is an estimate that is not adjusted (corrected) for confounding. Sullivan and Cowling[24] point out that a crude VE estimate express the correlation of vaccination with influenza, but may not be an accurate estimate of the causal effect of vaccination on the risk of influenza.

**Pooling of several individual studies**

*Pooled estimate*

In the aggregate-data meta-analysis, VE estimates from individual sites are combined into a weighted average of the individual estimates. The major advantage of a meta-analysis is the increased power it has compared to individual studies (i.e. the probability to detect an effect of vaccination if such an effect is present).

*Between-study heterogeneity*

Statistical heterogeneity refers to the variability between influenza vaccine effectiveness estimates in studies included in the aggregated data meta-analysis that goes beyond variability expected due to chance[25]. Sources of heterogeneity include bias, true underlying differences in vaccines effectiveness from country to country (e.g. due to differences in population or influenza strain circulation), bias, chance, and methodological factors. The pooled estimate has been calculated using a random-effects model, which assumes VE can vary due to underlying difference in vaccine effectiveness and chance[26]. To minimize the impact of differences in methodology on multicentre VE estimates, protocols should be harmonized.

An indication for the heterogeneity among estimates from different study sites is obtained by calculating I2. The I2 statistic is to be interpreted as the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies. Low, moderate and high levels of heterogeneity correspond to I2 values of 25%, 50% and 75%, respectively. Generally, the lower the heterogeneity, the more meaningful the pooled estimate as a description of vaccine performance. In case I2 is high, it is worthwhile to explore sources of heterogeneity.

**Cross-season IVE analysis**

Cross-seasonal IVE analysis are an alternative way of summarizing effectiveness data over a period of time and perform studies on the effect of influenza vaccination in previous seasons and waning effect of influenza vaccines.

DRIVE did not finally performed a cross seasonal IVE analysis.

# 2. Communicating IVE results

The interpretation of vaccine effectiveness results goes hand in hand with communicating them to various stakeholder groups including healthcare professionals, decision-makers, regulators, media and the general public. To understand the communications methods and needs, DRIVE Work Package 5: Communication and dissemination of results has developed a web-based survey directed at the “level 1” stakeholders identified in D5.1: Communication of a detailed stakeholder map for the DRIVE Project, which includes the identification, grouping and layering of all stakeholders. In addition to the information gained by the survey, the materials provided by public health authorities such as the NHS, ECDC and CDC have been analysed. During the 5-years development of DRIVE, WP5 has gathered information of the different stakeholder groups’ needs and sought input from regulatory agencies and the public health community. DRIVE Communications plan also summarizes key messages in terms of IVE communication. ISC advise on how to present IVE results (not in favour of threshold for “precision”).

## 2.1 Describing VE verbally

Vaccine effectiveness may be defined as the fraction of influenza cases directly prevented by the vaccination (and not by other, indirect vaccine effects such as herd immunity). It is often described by a percentage (VE%): if in a population 15% of the unvaccinated people become infected with influenza compared to 6% of the vaccinated people, then the vaccine effectiveness is (15%-6%)/15% = 60%.

While VE% point estimates and corresponding confidence intervals are often used in scientific communications and within the public health community, it is important to communicate their meaning also in lay terms. However, a single set of guidelines to translate VE% into words may be difficult to establish, e.g. because the expected VE differs across groups of vaccinees (e.g. young vs. elderly adults) and because the uncertainty represented by confidence intervals needs to be taken into account. Consequently, establishing thresholds to define VE as good/precise/high or otherwise is challenging and rather arbitrary.

However, in order to guide the interpretation of numerous vaccine effectiveness estimates by brand, age and setting, DRIVE has applied a confidence interval width of <40% for the definition of precise estimates. The < 40% CI width threshold was proposed based on the IVE estimates annually generated, which are rarely below 20% or above 80% (unless there is an antigenic drift during the course of the season).

Although all IVE estimates are generated and presented in DRIVE reports and presentations, those which are considered “precise” as per DRIVE definition (<40% CI) are emphasized in the annual reports and are the only estimates presented in the lay summaries. The implementation of the <40% CI threshold as the DRIVE definition for “precise” VE estimate has been extensively discussed internally in the yearly DRIVE methods workshops with WP7 and EFPIA, with the Independent Scientific Committee and with regulators (EMA, Paul Ehrlich Institute). Up to date, no clear conclusion on the adequacy of the threshold has been reached. For future sample size calculations and IVE studies it would be ideal to determine what minimum precision is desired for action for regulators and for public health agents.

Other approaches to describe the impact of a vaccine include averted cases (e.g. influenza infections, hospitalizations or deaths) or the number needed to vaccinate (NNV) to avoid one outcome. Presented this way,

the information may be more concrete and easier to understand. However, additional information besides VE% (incidence of the event in question, vaccine coverage) is needed to provide these figures, and these may not be routinely or reliably available.

Whatever the chosen metric, it is not necessarily meaningful to evaluate the effectiveness of influenza vaccines on the same scale as with other vaccines. Even if the seasonal IVE would not be satisfactory during some years, the long-term effects of the vaccination will save lives especially in the vulnerable groups.

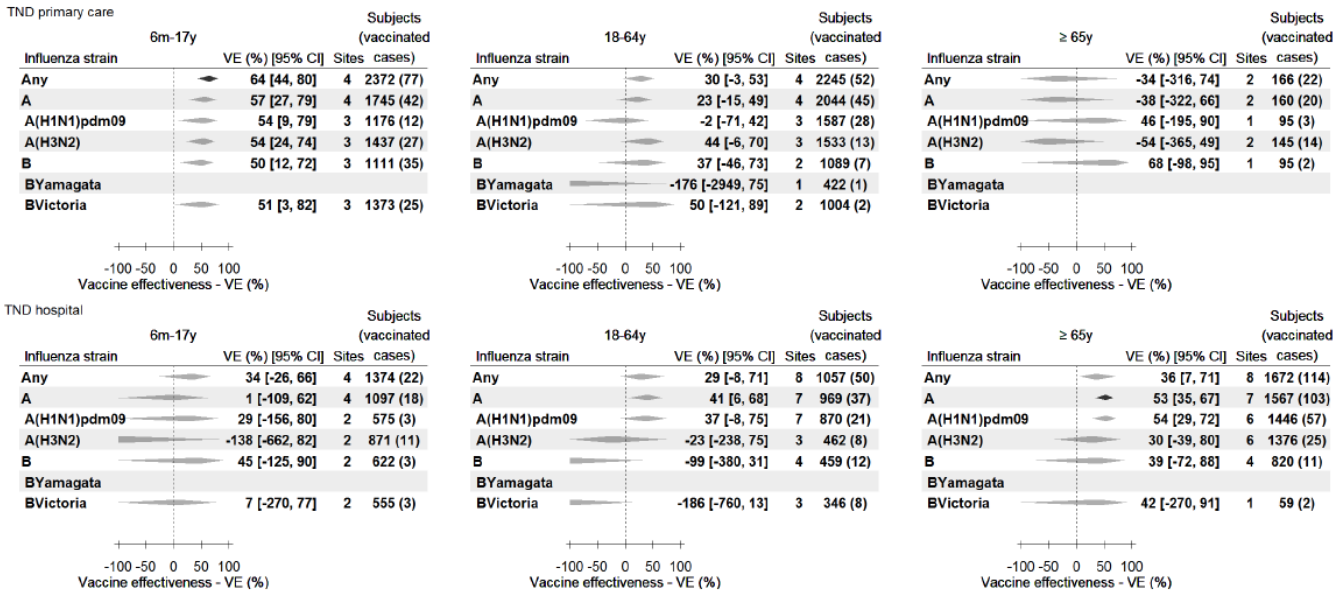
### 2.2 Presenting VE graphically

For communication purposes, clear infographics may be preferable to lengthy verbal descriptions. Examples of influenza infographics produced by public health authorities for a variety of stakeholders are listed below; however, many of these focus on trends in the circulation of influenza viruses or the burden of influenza; vaccine effectiveness is not necessarily included.

- ECDC
- FluNewsEurope
- EuroMOMO
- CDC
- THL

DRIVE scientific communications and annual results reports use forest plots to describe pooled influenza vaccine effectiveness estimates. This is a conventional way of presenting the results of a meta-analysis. In order to display efficiently the large number of IVE estimates generated in the pooled analysis, DRIVE implemented multi-panel forest plots (Figure 1), although the forest plots showing the results underlying each age/setting figures of the multi-panel (displaying both the site-specific and meta-analysis VE estimations) are also available in Annexes and Webannex (Figure 2).

a)




Dark grey diamond: precise results (width of CI < 40%). Light grey diamond: non-precise results.

b)

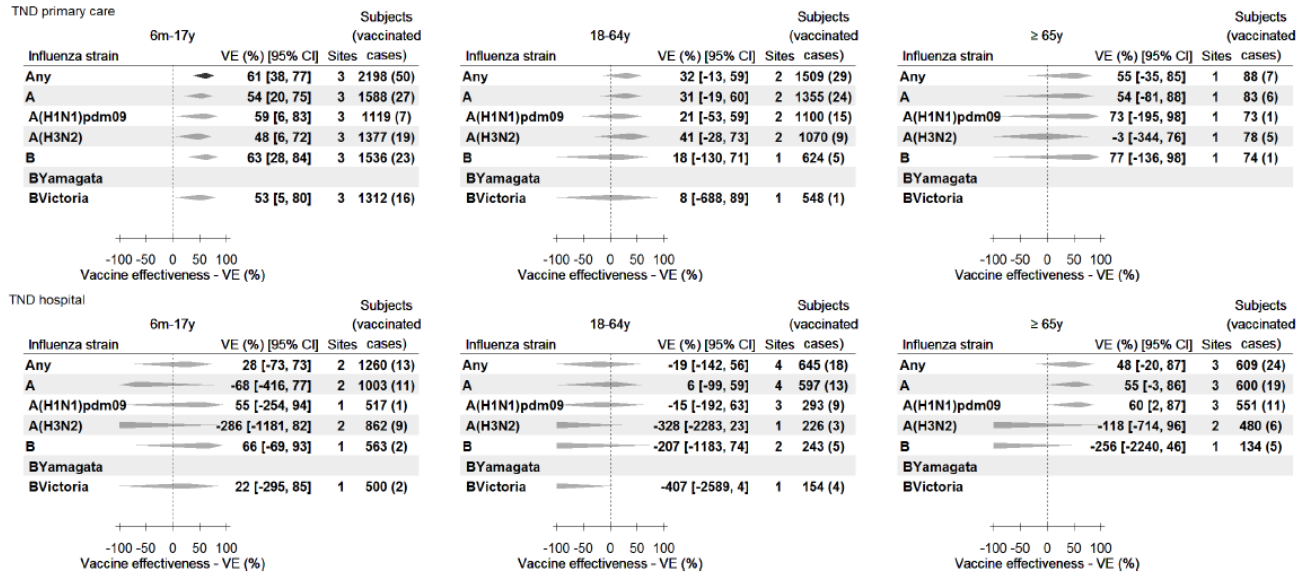



***Figure 1: Example of multi-panel forest plots for vaccine effectiveness graphic presentation from DRIVE report 2019/20.*** *The forest plots present: a) Any influenza VE: pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group. b) Brand-specific VE (Vaxigrip Tetra): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group. Black diamond indicates VE estimates with width of CI < 40% and light grey diamond VE estimates with width of CI > 40%*

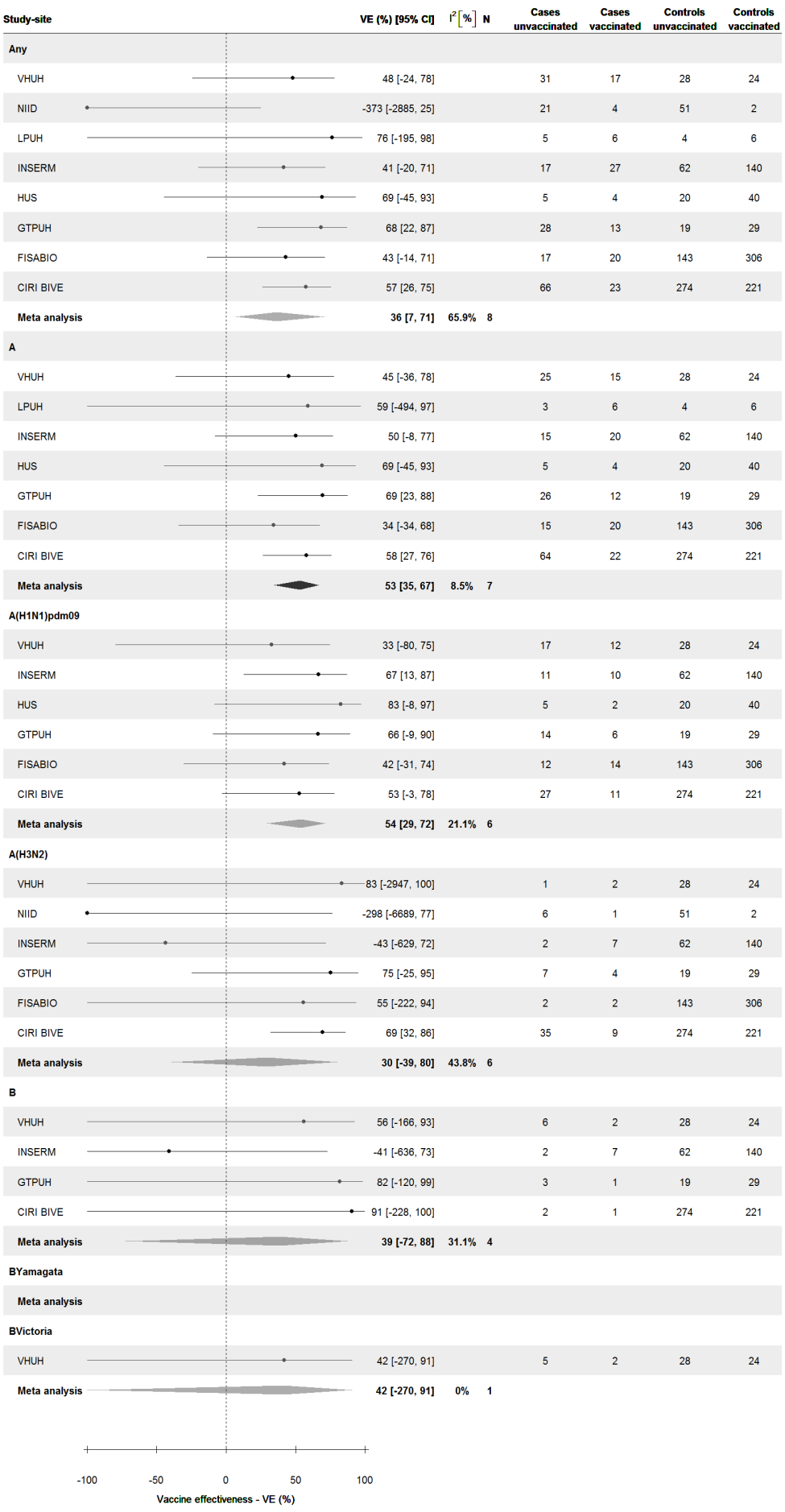

Study-site
VE (%) [95% CI]
I² [%]
N
Cases unvaccinated
Cases vaccinated
Controls unvaccinated
Controls vaccinated
Any
VHUH 48 [-24, 78] 31 17 28 24
NIID -373 [-2885, 25] 21 4 51 2
LPUH 76 [-195, 98] 5 6 4 6
INSERM 41 [-20, 71] 17 27 62 140
HUS 69 [-45, 93] 5 4 20 40
GTPUH 68 [22, 87] 28 13 19 29
FISABIO 43 [-14, 71] 17 20 143 306
CIRI BIVE 57 [26, 75] 66 23 274 221
Meta analysis 36 [7, 71] 65.9% 8
A
VHUH 45 [-36, 78] 25 15 28 24
LPUH 59 [-494, 97] 3 6 4 6
INSERM 50 [-8, 77] 15 20 62 140
HUS 69 [-45, 93] 5 4 20 40
GTPUH 69 [23, 88] 26 12 19 29
FISABIO 34 [-34, 68] 15 20 143 306
CIRI BIVE 58 [27, 76] 64 22 274 221
Meta analysis 53 [35, 67] 8.5% 7
A(H1N1)pdm09
VHUH 33 [-80, 75] 17 12 28 24
INSERM 67 [13, 87] 11 10 62 140
HUS 83 [-8, 97] 5 2 20 40
GTPUH 66 [-9, 90] 14 6 19 29
FISABIO 42 [-31, 74] 12 14 143 306
CIRI BIVE 53 [-3, 78] 27 11 274 221
Meta analysis 54 [29, 72] 21.1% 6
A(H3N2)
VHUH 83 [-2947, 100] 1 2 28 24
NIID -298 [-6689, 77] 6 1 51 2
INSERM -43 [-629, 72] 2 7 62 140
GTPUH 75 [-25, 95] 7 4 19 29
FISABIO 55 [-222, 94] 2 2 143 306
CIRI BIVE 69 [32, 86] 35 9 274 221
Meta analysis 30 [-39, 80] 43.8% 6
B
VHUH 56 [-166, 93] 6 2 28 24
INSERM -41 [-636, 73] 2 7 62 140
GTPUH 82 [-120, 99] 3 1 19 29
CIRI BIVE 91 [-228, 100] 2 1 274 221
Meta analysis 39 [-72, 88] 31.1% 4
BYamagata
Meta analysis
BVictoria
VHUH 42 [-270, 91] 5 2 28 24
Meta analysis 42 [-270, 91] 0% 1
-100
-50
0
50
100
Vaccine effectiveness - VE (%)

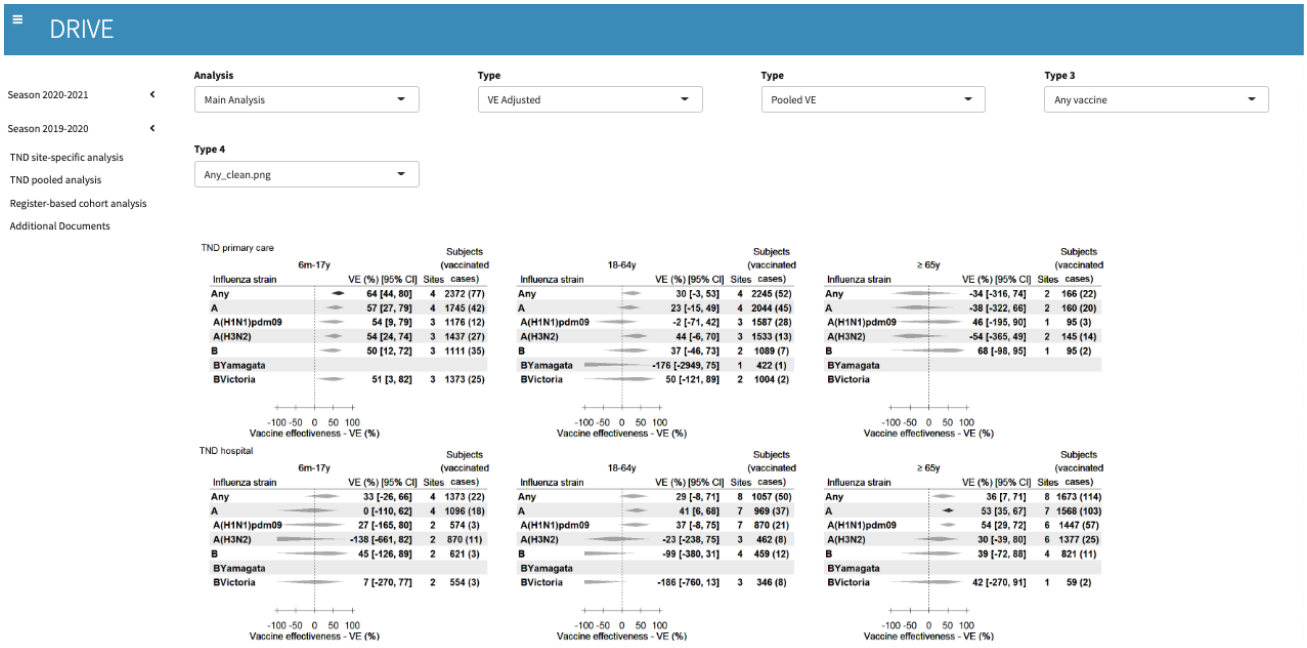
***Figure 2:*** *Example of forest plot displaying adjusted overall IVE estimates against any influenza, influenza types and subtypes at the hospital setting in the >65 years old age group. Site specific and pooled (meta-analysis) VE estimations are displayed for each of the outcomes. The % of VE and its associated confidence interval (CI) are presented, as well as the $r^2$ in % for the meta-analysis. Since the 2019/20 season, all the single-panel forest plots can be found in the DRIVE Webannex at the URL. https://apps.p-95.com/drivewebapp/.*

The DRIVE WebAnnex is a user-friendly web-application where all the results of the seasonal analyses are available (Figure 3). This is accessible at https://apps.p-95.com/drivewebapp/ and was built in summer 2020 to accompany the 2019/20 report. The Webannex had three main objectives:

- To facilitate the access to the results presented in the Annexes for readers (raw data and vaccine effectiveness estimates), making the project outcomes more FAIR (Findable, Accessible, Interoperable and Reusable), which is an essential part of DRIVE's open data strategy.
- To improve the visual presentation of the vaccine effectiveness estimates
- To reduce time required to update the Annexes after any changes to the results during the review process

The Webannex was also implemented for the 2020/21 and 2021/22 reports and has been improved by adding a functionality to download individual tables.

***Figure 3:*** *Screenshot from DRIVE's Webannex.*




## 2.3 Communicating to specific target groups

Some general recommendations of communicating IVE (e.g. the use of clear and concise language) are true for all stakeholders; others are more specific to the various stakeholder groups.

Public health institutes

Public health institutes (PHIs) have often a crucial role in informing vaccination policy and providing guidance to clinicians, and need vaccine effectiveness results to fulfil these tasks. Some, but not all, carry out their own vaccine effectiveness studies.

Based on the results of the DRIVE communications survey, information communicated by the PHIs comprises the burden of influenza illness, the benefits of influenza vaccines in general, and in some cases, IVE results in particular. The target groups for communication range from social and health care professionals to medical schools, media and the general public. The communication methods include publications in peer reviewed journals, national and international conferences, direct weekly reports, and websites. Some public institutions offer separate information pages for general public and health professionals, and display the VE% only on the professionals' section. Nevertheless, they use various phrases to communicate that while the vaccine does not offer perfect protection, there are several reasons to get it all the same (milder illness that otherwise etc.). Some stress the number of flu-related deaths in children. Many offer links to scientific articles.

Some PHIs that have answered the DRIVE communications survey have highlighted unanswered needs in IVE results (e.g. unavailability of IVE by age group, IVE of different vaccine types and brands, or IVE according to geographic area and severity of influenza).

Decision makers

Ministries of health and comparable political bodies are expected to share many of the same information needs as public health institutes. Especially in countries where vaccine purchases are centrally organized, the decision makers need vaccine effectiveness estimates for cost- effectiveness calculations and to direct vaccination programmes. (See also DRIVE D3.1: "Report on the sources for usage of specific influenza vaccine brands and accessibility for country-to-country differences in vaccine purchase and delivery systems" and DRIVE's publication "Investigating the procurement system for understanding seasonal influenza vaccine brand availability in Europe")

When communicating IVE to decision-makers, economic scenarios and the aspect of saved resources (in terms of e.g. averted hospitalizations and sick leaves) may be more relevant than with other stakeholders.

Healthcare professionals

In most countries, healthcare professionals such as doctors and nurses have a major role in providing vaccines and carrying out vaccination programmes. In order to perform these roles, they need to be aware of the incidence and potential severity of the influenza illness.

In addition to providing vaccine effectiveness figures, it is also important to address other issues such as perceived concerns over vaccine safety. Easy-to-understand measures of vaccine effectiveness and tools such as infographics may help in communicating the benefits of influenza vaccination to patients.

General public and media

The general public – representing all stakeholder groups outlined above as well as the targeted groups for influenza vaccination (that differ somewhat between countries) – are the people to finally make the choice of whether to get vaccinated. The media, on the other hand, can be an important partner in communicating influenza-related messages including vaccine effectiveness.

When communicating to the media or the general public, some PHIs choose to not emphasize the exact vaccine effectiveness figures focusing rather on the more general messages of protecting oneself and others through vaccination. The use of clear (and sometimes colloquial, e.g. "flu jab") terminology is important.

The ability of media to spread influenza-related messages is often greater than that of public institutions. News stories often capture stories of human interest; therefore, it can be useful to liaison with healthcare professionals "in the field" who can tell how the seasonal epidemic is being experienced on the local level. News stories also tend to seek novel or unexpected angles to the influenza epidemic.

During its last year, DRIVE has put emphasis on improving its communications at a European citizen level to raise awareness about the use of influenza vaccines and seek the partnerships with different patient organizations. In that context, DRIVE managed to engage with four patient organizations (PO) all over Europe (CiaoLapo, ApoyoPositivo, Active Citizenship Network and Coalition for Life-Course Immunisation). The main objective of this collaboration was to improve the understanding and the communication needs on IVE among the general public, and to get the point of view of patients.

The emergence of the SARS-CoV-2 pandemic in early 2020, has substantially changed the perception of the general public towards respiratory viral infections and its prevention. After the administration of COVID-19 vaccines in massive vaccination campaigns, they have shown generally a high but changing effectiveness, depending on circulating variants and population characteristics. More than ever, vaccine effectiveness is in the spotlight. Thus, IVE will be much more scrutinized by the general public from now on and it will be necessary to improve the communication on the particularities of influenza vaccines effectiveness.

Regulators

After the pilot season of 2017/18, DRIVE engaged in dialogue with the European Medicines Agency and other relevant regulatory agencies (e.g. Paul Ehrlich Institute). DRIVE has succeeded in establishing a regular dialogue with the EMA, although the brand-specific VE estimates produced during the project's lifetime have not been robust enough to fulfil the regulatory requests.

A formal National Scientific Advice with the Paul Ehrlich Institute took place in December 2020 and one of the discussed topics revolved around the definition of "precise" VE estimate and the adequacy of the threshold established by DRIVE for regulatory decision-making. Similar discussions have also been engaged with EMA.

More specifically, the Paul Ehrlich Institute experts pointed out that it is good to establish a boundary but requested DRIVE to provide the rationale of choosing 40% CI width. DRIVE generates a multitude of brand-specific IVE estimates, some of them more robust than others – as DRIVE is transparent and communicates all the estimates but would like to provide more credit to those with more precision. That is why 40% was considered precise enough in order to communicate and discuss the brand-specific IVE results. To the best of our knowledge there is no gold standard in the literature that would allow to define objectively what is a precise/robust estimate, so it will be essential to determine what cut-off precision can be considered acceptable from the regulatory or public health point of view.

# 3. Conclusion

DRIVE has successfully produced and communicated influenza vaccine effectiveness outputs during the 5 years lifetime of the project. From the first pilot season (2017/18) to the final season (2021/22), DRIVE has been adapting the way of interpreting and presenting IVE results, and produced overall and brand-specific IVE estimates with different levels of robustness in every season, with the exception of the season 2020/21 in which influenza did not circulate and only overall IVE estimates with very wide confidence intervals were produced for the Finnish cohort study, but not for the TND studies.

As a summary for interpreting IVE estimates, and recapping the lessons learnt from DRIVE, it is crucial to:

- Consider the characteristics of the study, which has been revised every season by updating the DRIVE core study protocols:
    - Study setting and population
    - Study design (case control, test-negative design, cohort…)
    - Outcome studied
    - Stratifications used

- Assess the strengths and limitations of the study:
  - Generalizability
  - Sample size and confidence intervals
  - Completeness of information
  - Bias and confounding
- Consider the vaccines used and seasonal vaccine match:
  - Vaccine type (technology platform, valency, culture…)
  - Vaccine viral strain composition (WHO recommendation)
  - Pattern of virus circulation using surveillance data
  - Interference with other respiratory viruses (SARS-CoV-2 impact)
- Translate the IVE estimate into concrete terms:
  - Verbal description
  - Graphic presentation of IVE results (forest plots)
  - Infographics
  - Outcomes averted (infections, medically attended visits, hospitalizations, deaths)
  - Cost-effectiveness
  - In relation to other published estimates (if comparable)
- Adapt the communication to the specific needs of the audience.

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## Abbreviations

| | |
|---|---|
| ADVANCE | Accelerated Development of Vaccine benefit-risk Collaboration in Europe |
| ARI | Acute respiratory infection |
| CI | Confidence intervals |
| CVV | Candidate vaccine virus (CVV) |
| DRIVE | Development of Robust and Innovative Vaccine Effectiveness |
| EHR | Electronic healthcare records |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| GP | General practitioner |
| HA | Hemagglutinin |
| I-MOVE | Influenza - Monitoring Vaccine Effectiveness |
| ILI | Influenza-like illness |
| IVE | Influenza vaccine effectiveness |
| MAH | Marketing Authorization Holders |
| OR | Odds ratio |
| PCR | Polymerase chain reaction |
| PHI | Public Health Institutes |
| POC | Point-of-care |
| RR | Relative risk |
| RT-PCR | Real-time polymerase chain reaction |
| SAP | Statistical Analysis Plan |
| SARI | Severe acute respiratory infection |
| TND | Test-negative design |
| VE | Vaccine effectiveness |
| WHO | World Health Organization |
| WP | Work Package |